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NEWS 14 Oct 09 Korean abstracts now included in Derwent World Patents
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NEWS 15 Oct 09 Number of Derwent World Patents Index updates increased
NEWS 16 Oct 15 Calculated properties now in the REGISTRY/ZREGISTRY File
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NEWS 18 Oct 22 DGENE GETSIM has been improved

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=> s valsartan/CN

L1 1 VALSARTAN/CN

=> s L1

L2 1 VALSARTAN/CN

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L3 233 L1

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2258454 STRUCTURE

(STRUCTURE OR STRUCTURES)

L4 9 L3 AND STRUCTURE

=> d l4 1-9 ibib abs abs

L4 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:311121 CAPLUS

DOCUMENT NUMBER: 135:251404

TITLE: Does protein binding modulate the effect of angiotensin II receptor antagonists?

AUTHOR(S): Maillard, Marc P.; Centeno, Catherine; Frostell-Karlsson, Asa; Brunner, Hans R.; Burnier, Michel

CORPORATE SOURCE: Division of Hypertension and Vascular Medicine, Lausanne University Hospital, Lausanne, CH-1011, Switz.

SOURCE: JRAAS (2001), 2(Suppl. 1), S54-S58

CODEN: JRAAAG; ISSN: 1470-3203

PUBLISHER: JRAAS Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Angiotensin II AT1-receptor antagonists are highly bound to blood plasma proteins (.gtoreq. 99%). With some antagonists, such as DuP-532, the protein binding was such that no efficacy of the drug could be demonstrated clin. Whether protein binding interferes with the efficacy of other antagonists is not known. The authors have therefore investigated in vitro how plasma proteins may affect the antagonistic effect of different AT1-receptor antagonists. A radio-receptor binding assay was used to analyze the interaction between proteins and the

ability

of various angiotensin II (Ang II) antagonists to block AT1-receptors.

In

addn., the Biacore technol., a new technique which enables the real-time monitoring of binding events between 2 mols., was used to evaluate the dissocn. rate consts. of 5 AT1-receptor antagonists from human serum albumin. The in vitro AT1-antagonistic effects of different Ang II receptor antagonists were differentially affected by the presence of

human

plasma, with rightward shifts of the IC50 ranging from 1 to several orders of magnitude. The importance of the shift correlates with the dissocn. rate consts. of these drugs from albumin. The authors' expts. also show that the way that AT1-receptor antagonists bind to proteins differs from

1 compd. to another. These results suggest that the interaction with plasma

proteins appears to modulate the efficacy of some Ang II antagonists. Although the high binding level of Ang II receptor antagonist to plasma proteins appears to be a feature common to this class of compds., the kinetics and characteristics of this binding is of great importance.

With some antagonists, protein binding interferes markedly with their efficacy to block AT1-receptors.

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REFERENCE COUNT: 12

REFERENCE(S): (1) Burnier, M; Lancet 2000, V355, P637 CAPLUS
(2) Chiu, A; Biochem Biophys Res Comm 1991, V177(1), P209 CAPLUS
(3) Csajka, C; Pharmacokinet 1997, V32, P1 CAPLUS
(4) Goldberg, M; Clin Pharmacol ther 1997, V61, P59 CAPLUS
(6) Maillard, M; Am J Hypertens 1999, V12, P1201 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:82589 CAPLUS

DOCUMENT NUMBER: 135:86860

TITLE: Antiplatelet action of losartan involves TXA2 receptor

AUTHOR(S): antagonism but not TXA2 synthase inhibition
Chlopicki, S.; Koda, M.; Chabielska, E.; Buczek, W.; Gryglewski, R. J.CORPORATE SOURCE: Department of Pharmacology Medical College,
Jagiellonian University, Pol.SOURCE: J. Physiol. Pharmacol. (2000), 51(4, Pt. 1), 715-722
CODEN: JPHPEI; ISSN: 0867-5910

PUBLISHER: Polish Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Various AT1 receptor antagonists including losartan are known to inhibit human platelet activation by antagonizing TXA2/PGH2 receptors (TP receptors). Presently, we check a hypothesis that losartan, an imidazole deriv. in contrast with valsartan, a non-imidazole compd., may inhibit human platelet activation also through inhibition of TXA2 synthesis. Inhibitory action of losartan, its active metabolite EXP 3174, and valsartan, on collagen-induced platelet aggregation and TXA2 generation was compared to effects achieved by each compd. on U 46619-induced aggregation in aspirinized platelets. Losartan and aspirin inhibited collagen-induced platelet aggregation with approx. the same potency, whereas EXP 3174 and valsartan showed much weaker antiplatelet effects. Interestingly, losartan, EXP 3174 and valsartan displayed similar potencies as inhibitors of U 46619-induced aggregation in aspirinized platelets as in collagen-induced aggregation in non-aspirinized platelets.

None of the above three AT1 antagonists, up to a concn. of 300 .mu.M, did influence collagen-induced TXA2 synthesis in human platelets. In conclusion, antiplatelet effects of AT1 antagonists, irresp. of the presence or absence of non-condensed imidazole in their chem.

structure, involve antagonism of TP receptors but not inhibition of TXA2 synthesis in platelets.

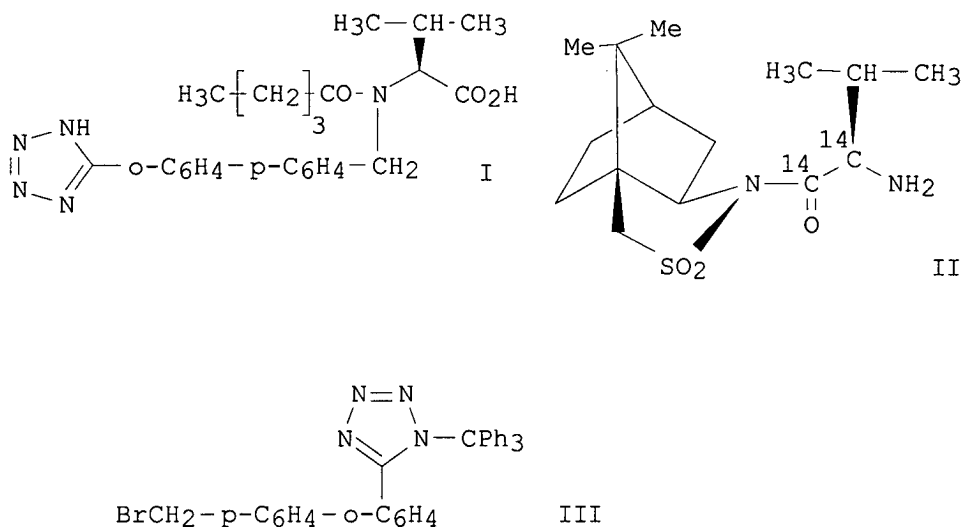
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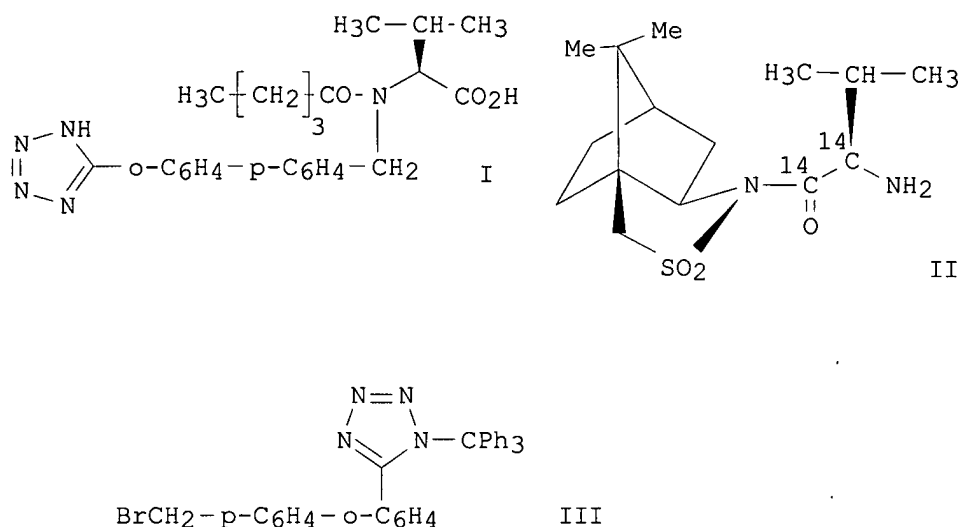
L4 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:805989 CAPLUS
 DOCUMENT NUMBER: 134:101153
 TITLE: Carbon-14 labelling of DIOVAN in its valine-moiety
 AUTHOR(S): Moenius, Th.; Voges, R.; Burtscher, P.; Zuger, Ch.
 CORPORATE SOURCE: Preclinical Safety, DMPK-IL, Novartis Pharma AG,
 CH-Basel, Switz.
 SOURCE: J. Labelled Compd. Radiopharm. (2000), 43(13),
 1245-1252
 CODEN: JLCRD4; ISSN: 0362-4803
 PUBLISHER: John Wiley & Sons Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB As a highly specific and non peptide AT₁-antagonist Valsartan (I) is marketed under the trade-name DIOVAN for effective treatment of hypertension. This paper describes the synthesis of ¹⁴C-labeled I, which incorporates two ¹⁴C isotopes in the valine-moiety. Reaction of (-)-bromo-[1,2-¹⁴C]acetyl bornane-10.2-sultam ((-)-[¹⁴C₂]BABS) with benzophenone imine gave (-)-diphenyl-methylene[1,2-¹⁴C₂]glycinyl bornane-10.2-sultam ((-)-[¹⁴C₂]DPMGBS), which was alkylated with 2-iodopropane to build-up the valine **structure**. Initially the resulting sultam-protected valine (II) was treated with treated with bromide (III) to produce the precursor. However, under conditions routinely used for sultam-cleavage deprotection resulted in the racemization of the amino acid. Successful cleavage was accomplished via N-Boc-protection of II followed by hydrolytic cleavage of the auxiliary and esterification to give the L-[¹⁴C₂]valine benzyl ester. Finally [¹⁴C₂]-I was synthesized in a 10 step synthesis in an overall radiochem. yield of 10% relative to the (-)-[1,2-¹⁴C]BABS employed.

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REFERENCE COUNT: 14
 REFERENCE(S): (2) Anon; US 4355040 CAPLUS
 (4) Buhlmayer, P; Bioorganic & Medicinal Chemistry Letters 1994, V4, P29 CAPLUS
 (5) Burtscher, P; J Labelled Cpd Radiopharm 2000, V43, P205 CAPLUS
 (6) Criscione, L; Cardiovascular Drug Reviews 1995, V13, P230 CAPLUS
 (7) de Gasparo, M; Regulatory Peptides 1995, V59, P303 CAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS
 ACCESSION NUMBER: 2000:476348 CAPLUS
 DOCUMENT NUMBER: 133:171982
 TITLE: Basilar artery remodelling in the genetically hypertensive rat: effects of nitric oxide synthase

inhibition and treatment with valsartan and enalapril
 AUTHOR(S): Ledingham, J. M.; Laverty, R.
 CORPORATE SOURCE: Department of Pharmacology, School of Medical
 Sciences, University of Otago, Dunedin, N. Z.
 SOURCE: Clin. Exp. Pharmacol. Physiol. (2000), 27(8), 642-646
 CODEN: CEXPB9; ISSN: 0305-1870
 PUBLISHER: Blackwell Science Asia Pty Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB 1. The **structure** of the basilar artery and the relationship of
structure to blood pressure and ventricular hypertrophy was examd.
 in genetically hypertensive (GH) rats, their control normotensive (N)
 Wistar strain, GH given the nitric oxide synthase (NOS) inhibitor,
 NG-nitro-L-arginine Me ester (L-NAME) and GH given L-NAME and either
 valsartan or enalapril. 2. Systolic blood pressure (SBP; tail-cuff) was
 measured weekly from age 7-12 wk. At the end of the expt. at 12 wk, the
 basilar artery was fixed by perfusion and embedded in Technovit (Heraeus
 Kulzer GmbH, Werheim, Germany). Serial sections were cut and stained and
 stereol. anal. applied to quantify the morphol. of the vessels. Left
 ventricular (LV) mass was detd. 3. Both SBP and LV mass were
 significantly increased in GH compared with N ($P < 0.001$) and increased
 further in GH given L-NAME ($P < 0.05$). The GH L-NAME + valsartan and GH
 L-NAME + enalapril groups had significantly lower ($P < 0.001$) SBP and LV
 mass than the GH L-NAME group. 4. Basilar arteries in GH (which are
 frankly hypertensive, but have no apparent endothelial defect) showed
 hypotrophic inward remodelling compared with the N control group with no
 change in media to lumen ratio. 5. In the GH L-NAME group, further
 inward remodelling occurred and the media to lumen ratio was increased compared
 with N ($P < 0.01$) and GH ($P < 0.05$). Valsartan treatment in GH L-NAME
 rats caused eutrophic outward remodelling. Enalapril caused hypertrophic
 outward remodelling, suggesting that the angiotensin II-stimulated growth
 was not entirely suppressed with an angiotensin-converting enzyme
 inhibitor or that there was a bradykinin effect with enalapril. 6. In GH
 with an endothelial defect induced by treatment with L-NAME, the further
 remodelling, together with an increased media to lumen ratio and the
 development of a stroke-like syndrome, indicates the NOS-inhibited GH rat
 may be a useful model for essential hypertension (where it is known that
 endothelial abnormalities exist) and where stroke can develop as a
 consequence of the hypertension.

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REFERENCE COUNT: 27
REFERENCE(S): (3) Blot, S; Stroke 1994, V25, P1666 CAPLUS
(4) Diederich, D; Ant J Physiol 1990, V258, PH445 CAPLUS
(11) Konishi, M; Hypertension 1983, V5, P881 CAPLUS
(12) Ledingham, J; Clin Exp Pharmacol Physiol 1997, V24, P433 CAPLUS
(14) Lee, R; Pharmacol Ther 1995, V66, P149 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:204117 CAPLUS
DOCUMENT NUMBER: 126:195243
TITLE: Method for treating renal disease using an ACE inhibitor and an angiotensin II antagonist
INVENTOR(S): Remuzzi, Giuseppe; Eydeloth, Ronald S.; Owen, Roger A.; Shahinfar, Shahnaz
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; Laboratoires Merck Sharp & Dohme-Chibret Snc; Remuzzi, Giuseppe; Eydeloth, Ronald S.; Owen, Roger A.; Shahinfar, Shahnaz
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9702032	A1	19970123	WO 1996-US10942	19960626
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RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
CA 2224451	AA	19970123	CA 1996-2224451	19960626
AU 9662916	A1	19970205	AU 1996-62916	19960626
AU 716519	B2	20000224		
EP 835106	A1	19980415	EP 1996-921794	19960626
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI			
JP 11508894	T2	19990803	JP 1996-505200	19960626
PRIORITY APPLN. INFO.:			US 1995-770	19950630
			GB 1996-2854	19960213

WO 1996-US10942 19960626

AB The present invention relates to a method of treating and/or preventing renal disease with the coadministration of an ACE inhibitor and an AII receptor antagonist. The present invention also relates to a method for protection of renal **structure** and/or renal function with the coadministration of an ACE inhibitor and an AII receptor antagonist. The combination is also useful in preventing renal injury and protecting glomerular **structure**. The effect of Lisinopril (ACE inhibitor) and Losartan (angiotensin II receptor antagonist) in animals with

diabetic
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nephropathy is described.

L4 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:50392 CAPLUS

DOCUMENT NUMBER: 126:139974

TITLE: A 3D QSAR CoMFA study of non-peptide angiotensin II receptor antagonists

AUTHOR(S): Belvisi, Laura; Bravi, Gianpaolo; Catalano, Giovanna; Mabilia, Massimo; Salimbeni, Aldo; Scolastico, Carlo

CORPORATE SOURCE: Organic and Industrial Chemistry Department, C.N.R. (National Research Council) Centre for the Study of Organic and Natural Compounds, University of Milan, Milan, I-20133, Italy

SOURCE: J. Comput.-Aided Mol. Des. (1996), 10(6), 567-582

CODEN: JCADEQ; ISSN: 0920-654X

PUBLISHER: ESCOM

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A series of non-peptide angiotensin II receptor antagonists was investigated with the aim of developing a 3D QSAR model using comparative mol. field anal. descriptors and approaches. The main goals of the study were dictated by an interest in methodologies and an understanding of the binding requirements to the AT1 receptor. Consistency with the

previously
derived activity models was always checked to contemporarily test the validity of the various hypotheses. The specific conformations chosen

for
the study, the procedures invoked to superimpose all **structures**, the conditions employed to generate steric and electrostatic field values and the various PCA/PLS runs are discussed in detail. The effect of exptl. design techniques to select objects (mols.) and variables (descriptors) with respect to the predictive power of the QSAR models derived was esp. analyzed.

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L4 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:29751 CAPLUS

DOCUMENT NUMBER: 126:98857

TITLE: Non-peptide angiotensin II receptor antagonists: PCA &

PLS analyses employing different types of 3D molecular

descriptors

AUTHOR(S): Mabilia, M.; Fioravanzo, E.

CORPORATE SOURCE: S.IN - Soluzioni Informatiche, Vicenza, I-36100, Italy

SOURCE: Bioact. Compd. Des. (1996), 127-136. Editor(s): Ford,

Martyn G. Bios Scientific Publishers: Oxford, UK.

CODEN: 63SXAI

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Different three-dimensional (3D) mol. descriptors were generated for a set

of angiotensin II receptor antagonists with the aim to: a. establish quant. **structure**-activity relationships (QSAR) by means of Principal Component Anal. (PCA) and Partial Least-Squares (PLS) methods, b. compare the modeling and predictive capabilities of the different

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L4 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:381984 CAPLUS

DOCUMENT NUMBER: 125:75808

TITLE: Remodelling of resistance arteries in genetically hypertensive rats by treatment with valsartan, an angiotensin II receptor antagonist

AUTHOR(S): Ledingham, Janet M.; Laverty, R.

CORPORATE SOURCE: Dep. Pharmacol., Univ. Otago Med. Sch., Dundee, N. Z.

SOURCE: Clin. Exp. Pharmacol. Physiol. (1996), 23(6/7),

576-578

CODEN: CEXPB9; ISSN: 0305-1870

DOCUMENT TYPE:

Journal

LANGUAGE:

English

AB In the present study, New Zealand genetically hypertensive (GH) rats were treated with valsartan, a specific angiotensin II (AT1) receptor antagonist, to measure the effects on blood pressure (BP), cardiac hypertrophy and the **structure** of resistance arteries. Normotensive (N) rats were used as controls. Valsartan (val) was given

to

GH rats at three different doses (10, 3 or 0.3 mg/kg per day, via osmotic mini-pumps implanted i.p.) from age 4-10 wk. Untreated GH (mini-pump + vehicle) and N rats (mini-pump + vehicle) were used as controls. BP was measured weekly and at the end of the expt., left ventricular (LV) mass was recorded and the **structure** of mesenteric resistance arteries (MRA) was detd. using stereol. methods. BP fell in a dose-dependent fashion, being reduced to normotensive levels by 10 mg/kg; LV mass was significantly reduced ($P < 0.0001$) to below normotensive values in the GH group given 10 mg/kg val and significantly reduced ($P < 0.001$), although not normalized, in the other two treatment groups. In MRA, the media/lm (M/L) ratio was reduced by val according to dose level, to below normotensive values in GHval10, and to levels not different from normotensive values in the GHval3 and GHval0.3 groups. The hypertrophy

of

smooth muscle cells in GH rats was reduced with val treatment at all doses. Reversal of cardiac and vascular hypertrophy occurred even when

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was not reduced to normotensive levels, indicating an effect on vessel growth but without any retardation of body growth. These results suggest that the vascular structural changes seen after val and angiotensin converting enzyme inhibitor treatment are probably due to the blocking of angiotensin rather than any bradykinin effect.

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ACCESSION NUMBER: 1994:260544 CAPLUS

DOCUMENT NUMBER: 120:260544

TITLE: Valsartan, a potent, orally active angiotensin II antagonist developed from the structurally new amino acid series

AUTHOR(S): Buhlmayer, Peter; Furet, Pascal; Criscione, Leoluca; de Gasparo, Marc; Whitebread, Steven; Schmidlin, Tibur; Lattmann, Rene; Wood, Jeanette

CORPORATE SOURCE: Res. Dep., Ciba-Geigy Ltd., Basel, CH-4002, Switz.

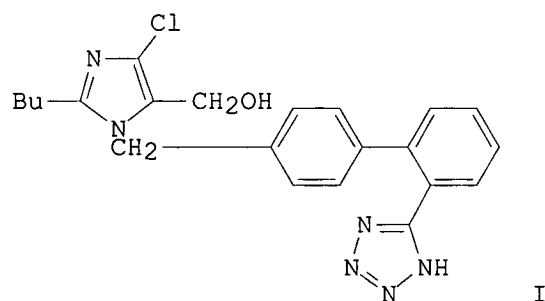
SOURCE: Bioorg. Med. Chem. Lett. (1994), 4(1), 29-34

CODEN: BMCLE8; ISSN: 0960-894X

DOCUMENT TYPE: Journal

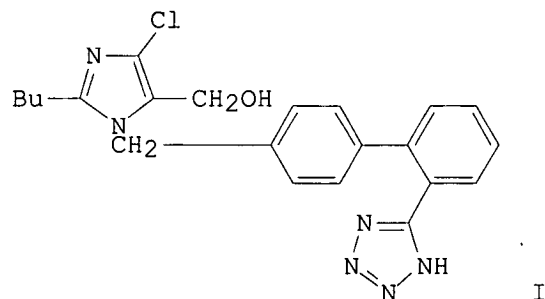
LANGUAGE: English

GI



AB Starting from the **structure** of DuP-753 (I) and a 3-dimensional model of the pentapeptide Tyr-Ile-His-Pro-Ile, a series of new and highly potent antagonist has been designed where the imidazole moiety of the DuPont compd. has been replaced by an N-acylated aminoacid residue. Valsartan (CGP48933) [(S)-N-valeryl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]valine], has been selected for clin. investigation.

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
22.42	30.79

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-5.29	-5.29

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